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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/694,519	10/23/2000	Robert Joseph Isfort	8311	9641

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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	12

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/694,519	ISFORT ET AL.	
	Examin r	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-14,18-26 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Office action is in response to an amendment filed on June 7, 2002.

Response to Arguments

2. Applicant's arguments filed on June 7, 2002 have been fully considered but they are not persuasive. Applicants argue that:

A) the enablement rejection is improper, because while the claimed compounds may act upon other receptors, the invention provides compounds selective for the VPAC receptors, and no undue experimentation would be necessary to establish their selectivity.

B) the art rejection over Gourlet et al. of claim 15 is improper, since while Gourlet et al. teach pharmaceutical compositions comprising peptides selective for the VPAC1 receptor, they do not teach using them for treatment of muscle conditions.

C) the art rejection of claims 16, 17 and 27 over Vittone et al., teaching improved muscle function after administration of GHRH, is improper, since the results of Vittone et al. were not obtained by interaction of a selective VPAC agonist with the VPAC receptor.

a. Considering the first argument, while it might not be undue experimentation to determine whether the claimed compounds are more selective for VPAC than for other receptors, it would still require undue experimentation to determine their therapeutic effects and side effects (see the discussion in the previous Office action). This rejection is maintained.

b. In response to applicant's argument that a rejection of claim 15 over Gourlet et al. is improper, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing

the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Since the peptides of Gourlet et al. are specific for the VPAC1 receptor, their administration would result in the claimed effects of treating muscle diseases. The rejection is maintained.

c. Applicants assert that GHRH is selective for the VPAC receptors, therefore an argument that the rejection of claims 16, 17 and 27 over Vittone et al. is improper contradicts this assertion. The rejection is maintained.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 15-17 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for VPAC (vasoactive intestinal peptide) receptor agonists specific for either $VPAC_1$ ([K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2]), $VPAC_2$ (Ro 25-1553) or both (PACAP-38), pituitary adenylate cyclase-activating polypeptide) receptors, does not reasonably provide enablement for any other compound or any of the other agonists listed in claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not provide any indications that VPAC receptor agonists such as VIP (vasoactive intestinal peptide), PACAP-27, helodermin, peptide histidine isoleucine amide (PHI), peptide histidine methionine amide (PMI), peptide histidine valine amide (PVI), growth hormone

releasing hormone (GHRH, GRH, GRF), secretin, glucagon, (Arg15, Arg21) VIP, [Arg 15,20,21, Leu17]-VIP-Gly-Lys-Arg-NH_2, multimeric VIP fusion protein, Ro-1392, PACAP(6-38) when administered to a subject would result in an increase of the skeletal muscle mass or function.

The agonists of VPAC receptors listed above are related to VIP, whose receptors are widely distributed in the central and peripheral nervous system and in plasma membranes of many organs and tissues (gastrointestinal tract, lung, heart, uterus, adrenal, adipocytes, enterocytes, hepatocytes, liver, etc.). VIP has a broad range of biological actions, such as vasodilation of vessels, brochodilation, relaxation of various muscles (esophageal sphincter, fundic muscle, gallbladder smooth muscle, colonic smooth muscle of the intestines), glycogenolysis and lipolysis, bone resorption, release of insulin, glucagon, or somatostatin in the pancreas, stimulation of prolactin, growth hormone (GH) release in the pituitary, etc. (Said, J. Endocrinol. Invest., vol. 9, p. 191-200, 1986).

In addition, helodermin, glucagon, GRF, secretin have their own specific receptors, but also bind to the VIP receptors. For example, secretin, GRF, PHI and helodermin bind to the VIP receptor, VIP, GRF, PHI and helodermin bind to the secretin receptors (in pancreas and exocrine cells), glucagon binds to its receptors in the liver, and GRF to its receptors in the pituitary gland (Laburthe et al., Ann. NY Acad. Sci., vol. 527, pp. 296-313, 1988, see Fig. 9). GRF and PHI were found to be VIP receptor agonists (Emami et al., Peptides, vol. 7, pp. 121-127, 1986, see Abstract), and PHM was found to be a VIP agonist with low potency on human VIP receptors (Laburthe et al., Life Sci., vol. 36, pp. 991-995, see Abstract).

PACAP-38 and PACAP-27 in addition to binding to their own receptors bind to the VIP receptors (Ulrich et al., Gastroenterology, vol. 114, pp. 382-397, 1998, see page 387, third paragraph).

Therefore, taking all of the above facts into account, administration of any of the above VPAC agonists, despite the fact that they are related, cannot be predicted to have an effect of increasing muscle strength or function, and may potentially lead to harmful outcome, as they also target other receptors. As noted by Musso et al. (U.S. Patent No. 4,835, 252): " ...the naturally occurring VIP has so many biological activities that its use is limited, because beneficial effects are associated unavoidably with significant, deletorious side effects, especially when the VIP is administered intravenously..." (col. 2, lines 27-31).

Due to the large quantity of experimentation necessary to establish whether the administration of compounds other than [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38 would result in an increase of muscle mass or function, the lack of direction/guidance presented in the specification regarding administration of compounds other than [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38 resulting in an increase of muscle mass or function, the lack of working examples directed to the administration of compounds other than [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38 and resulting increase of muscle mass or function, the complex nature of the invention (agonist binding to several receptor types), the unpredictability of the effects of the administration of compounds other than [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38 on an increase of muscle mass or function (see discussion above), undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Gourlet et al. (WO 98/02453).

Gourlet et al. teach peptides which are highly selective for the VIP1 (=$VPAC_1$) receptor, are agonists or antagonists, and pharmaceutical compositions comprising the peptides and pharmaceutically acceptable carrier (page 4, lines 8-11; page 5, lines 14-29; page 9, lines 17-24).

7. Claims 16, 17 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Vittone et al. (Metabolism, vol. 46, pp. 89-96, 1997).

Vittone et al. teach improved muscle function in elderly men (who suffer from the decrease in muscle mass and strength due to age-related decrease in growth hormone, GH, and insulin-like growth factor-I, IGF-I) after administration of single nightly injections of GHRH (Abstract; page 94, paragraph 4).

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS
August 7, 2002 TS

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
8/6/02